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Neuromyelitis optica, systemic sclerosis, and localized scleroderma: an integrative review

Neuromielite óptica, esclerose sistêmica e morfeia: uma revisão integrativa

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KEYWORDS:

Neuromyelitis optica; Systemic scleroderma; Localized scleroderma; aquaporin 4; Antibody.

ABSTRACT

Objectives: To assess whether systemic and localized sclerosis have a significant correlation with neuromyelitis optica and its spectrum of diseases, aiming to open new study perspectives for these autoimmune diseases. **Methods:** This is an integrative review of the literature of the last 20 years, which aims to investigate the relationship between neuromyelitis optica, systemic scleroderma, and localized scleroderma. Articles in Portuguese, English, and Spanish from the MEDLINE, LILACS, SciELO, and Scopus databases were searched using the keywords "neuromyelitis optica," "systemic scleroderma," and "localized scleroderma," along with their synonyms and correspondents in Portuguese and Spanish. **Results:** The search generated 23 articles. Three case reports, one in English and two in Portuguese, comprised the final corpus of this work. **Discussion:** The relationship between neuromyelitis optica and autoimmune diseases is well established, but its association with systemic and localized scleroderma is rarely reported in the literature. Furthermore, the reported associations primarily arise from isolated cases, thereby making this association relatively rare. Uncommon testing, the subclinical or initial status of some neuromyelitis optica presentations, and immunosuppressive therapies may explain this rare association. **Conclusion:** Active search and measurement studies of anti-aquaporin 4 in patients with autoimmune disorders are necessary. This is a large field of research that requires further investigation.

PALAVRAS-CHAVE:

Neuromielite óptica; Escleroderma sistêmico; Esclerodermia localizada; Aquaporina 4; Anticorpo.

RESUMO

Objetivos: Neuromielite óptica é uma doença imunomediada cujo diagnóstico baseia-se na detecção do anticorpo anti-aquaporina 4. A neuromielite óptica é reconhecidamente associada a uma gama de doenças autoimunes. **Métodos:** Trata-se de uma revisão integrativa da literatura dos últimos 20 anos que busca investigar a relação entre a neuromielite óptica e o escleroderma sistêmico e a esclerodermia localizada. Incluiu-se artigos em português, inglês ou espanhol das bases de dados MEDLINE, Lilacs, SciELO e Scopus encontrados através das palavras-chave "Neuromielite óptica", "Escleroderma Sistêmico" e "Esclerodermia Localizada", seus sinônimos e correspondentes em inglês e espanhol. **Resultados:** A busca gerou 23 artigos. Três relatos de caso, um em inglês e dois e português, compuseram o corpus final deste trabalho. **Discussão:** A relação entre Neuromielite óptica e doenças autoimunes é estabelecida. Em relação ao escleroderma sistêmico e a esclerodermia localizada há pouca associação dentro da literatura, maioria oriunda de casos isolados, dando a esta associação o status de raridade. A baixa testagem, status sub-clínicos/iniciais de algumas apresentações da neuromielite óptica e terapias imunossupressoras podem explicar esta baixa associação. **Conclusão:** Estudos de busca ativa e mensuração do anti-aquoporina 4 em pacientes com afecções auto-imunes se fazem necessários. Trata-se de um grande campo de pesquisa ainda a ser desbravado.

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INTRODUCTION

Neuromyelitis optica (NMO) is an inflammatory autoimmune demyelinating disease with severe clinical repercussions[1]. Its lesions are predominantly in the optic nerve and spinal cord, normally sparing the brain, unlike multiple sclerosis[2], of which NMO was once considered a localized variant[1]. Until 2004, the diagnosis of NMO was based on minor, major, and paraclinical criteria[3], but the discovery of an antibody against the aquaporin 4 (AQP4) water channel protein (NMO–IgG) changed the approach to the disease as follows: immunoglobulin was consequently considered as its main etiologic agent, with high specificity and sensitivity[4], which made early diagnosis possible and provided better treatment and prognosis for patients with NMO[1].

AQP4 is the main water channel protein of the central nervous system (CNS) and is located in astrocytes. It is responsible for brain fluid balance and control of serum potassium and glutamate levels[2,5,6]. The binding of anti-aquaporin 4 antibodies leads to a downregulation of these channels and causes astrocytic and, consequently, neuronal damage. In addition, it is responsible for generating inflammatory processes via complement and cellular immunity, demyelination, and edema in the CNS[6,7]. Furthermore, it is argued that NMO-IgG increases the permeability of the blood-brain barrier, allowing antibodies, granulocytes, and T-cell-specific antigens to enter this normally inaccessible environment[8].

Notable, the discovery of NMO–IgG has opened a new field of study, as the same antibody was identified in other autoimmune diseases, thereby creating the concept of NMO Spectrum Disorders (NMOSD)[1,9]. NMOSD include myasthenia gravis, hypothyroidism, pernicious anemia, scleroderma, ulcerative colitis, primary sclerosing cholangitis, idiopathic thrombocytopenic purpura, Sjögren's syndrome, sarcoidosis, antiphospholipid antibody syndrome, and systemic lupus erythematosus[10,11]. The possible mechanism of association between these autoimmune diseases remains under intense scientific investigation[12].

Scleroderma is one of the diseases under investigation in this scenario. It is an immune-mediated disorder of connective tissues with a wide spectrum of clinical presentations, characterized by sclerosis resulting from collagen deposition[13]. It can only affect skin, fascia, muscle, and bones, and in such cases it is characterized as localized scleroderma (LS), also known as morphea; alternatively, it is defined as systemic sclerosis (SS) when it expands and affects internal organs[14].

Of the several pathophysiological mechanisms proposed to explain the disease, the most accepted mechanism is as follows: circulating dysfunctional endothelial progenitor cells would exacerbate vascular deterioration, thereby generating vascular and SS[15].

Recent studies have demonstrated that dysregulation in the expression of aquaporins in dermal fibroblasts and in the microvascular endothelium may also be responsible for the fibrosis observed in these conditions. The aquaporin 1 channel, for example, participates in angiogenesis and in extracellular matrix remodeling, and it is highly expressed in patients with SS[16].

Another pathophysiological situation occurs with aquaporin 3 channels, which participate in skin healing and dehydration processes that are directly related to the pathophysiology of SS, leading to an underexpression of these channels being observed in these patients[17].

Furthermore, neurological involvement in patients with SS or LS was previously considered rare and incidental; however, new studies have shown that approximately 40% of these patients present this association, ranging from mild headaches to severe myopathies. The inflammatory activity of SS is theorized to contribute to the CNS damage observed in NMOSD[18].

It is evident that these diseases have a complex pathophysiology that is known to be associated with immunological and inflammatory mechanisms[17], and share receptors from the same family, with similar structure and functions, in addition to still unknown factors. Therefore, the purpose of this study was to assess whether-in a manner similar to other autoimmune and immune-mediated diseases-systemic and localized sclerosis would be diseases with a significant correlation with NMO/ NMOSD, to open new study perspectives for these autoimmune diseases.

METHODS

This is an integrative literature review. The articles were selected from the MEDLINE (Online System of Search and Analysis of Medical Literature), SciELO (Scientific Electronic Library Online), LILACS (Latin American and Caribbean Literature in Health Sciences), and Scopus databases. All articles published in Portuguese, English, or Spanish in the last 20 years

are selected. The keywords used were "neuromyelitis optica," "systemic scleroderma," and "localized scleroderma," as well as their respective synonyms and terms in Portuguese and Spanish. Clinical studies, case reports, cohort studies, and case-control studies were included. Integrative reviews, narratives, letters to the editor, and articles unavailable in full text were excluded.

RESULTS

The search generated a total of 23 articles (7 articles in the Pan American Health Organization's Virtual Health Library [VHL] search engine, which provides access to MEDLINE, LILACS, and SciELO, and 16 in the Scopus database). After the exclusion of duplicate articles, the articles obtained were read, eliminating those that did not match the subject or did not meet the established inclusion criteria (Figure 1).

Finally, 3 articles were selected, whose main data will be summarized in Table 1 below.

DISCUSSION

Approximately 20%–30% of NMO carriers have other autoimmune disorders[20], of which systemic lupus erythematosus, Sjögren's syndrome, rheumatoid arthritis, myasthenia gravis, and ulcerative colitis stand out as those with the highest correlation[1], but the association of NMO with SS and LS is somewhat infrequent. The present review focused its efforts on elucidating this gap.

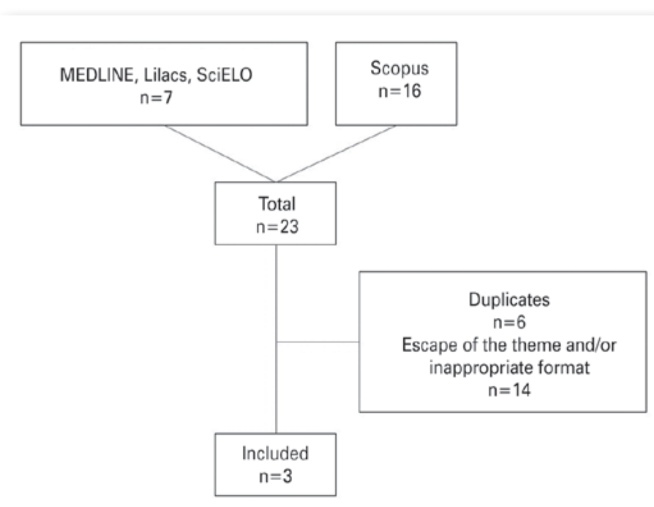


Figure 1. Flowchart of the article selection process using the MEDLINE, SciELO, LILACS, and Scopus databases, with the number of articles selected at each stage of the study

Three case reports constitute this review's final study material. The first case was a 44-year-old woman whose main complaint was the onset of intractable hiccups, vomiting, and dysphagia. The patient's skin appeared to be thickened bilaterally at the metacarpophalangeal junctions, and she also presented Raynaud's phenomenon. Subsequently, the patient developed blurred vision, muscle weakness, hypertonia, paroxysmal tonic spasms, Babinski's sign, and paresthesia in the lower limbs. Magnetic resonance imaging (MRI) demonstrated hyperintense foci in the periventricular white matter and in the spinal cord between C2 and C6. Antinuclear antibodies, anti-RNA polymerase III, antitopoisomerase I, and NMO–IgG all tested positive, thereby establishing the diagnosis of NMO. Intravenous administration of methylprednisolone was initiated, which brought about a significant degree of clinical improvement. On the fifth day of hospitalization, the patient had a hypertensive crisis and acute kidney injury, which required urgent hemodialysis. A biopsy was performed, confirming the diagnosis of a corticosteroid-induced scleroderma renal crisis. The patient was subsequently treated with other drugs, responding well to rituximab[18].

Another case was a 39-year-old woman with a history of NMOSD since 12 years before the study duration, when she had quadriplegia, MRI with cervical transverse myelitis, and positive anti-AQP4. On that occasion, she responded positively to pulse therapy with methylprednisolone and azathioprine. She was then referred for rheumatologic evaluation owing to skin thickening and Raynaud's phenomenon 1 year prior. Physical examination revealed telangiectasias on the face, leukomelanoderma on the chest, digital microulcerations, and diffuse skin thickening, with a modified Rodnan skin score of 22[17].

The patient had antinucleolar factor >1/1280, negative anti-Scl70, and a scleroderma pattern in nailfold capillaroscopy. Visceral involvement was ruled out, and the diagnosis of diffuse SS was confirmed using the ACR/EULAR criteria (2013). Monthly intravenous cyclophosphamide was then introduced, and after 8 months of treatment there was significant degree of skin improvement[17].

Finally, the last case analyzed was the report of a HCCP 54-year-old man, smoker, hypertensive, who had undergone a prostatectomy for cancer 2 years prior. Nearly 8 months previously, the patient presented rapidly progressing plaque scleroderma in the lower and upper limbs and in the abdomen. A skin

Table 1. Main information of the articles included for final analysis

Title	Authors	Year of publication	Database	Method	Objective	Results	Conclusions
Demyelinating syndrome in systemic sclerosis and neuromyelitis optica	Khaled Deeb, Jessika Eby e Jose Labault-Santiago.	2019	MEDLINE	Case report	Report a case of a patient with intractable hiccups, vomiting that evolves with paraplegia. MRI compatible with transverse myelitis and positive NMO-IgG.	SS was superimposed by a scleroderma renal crisis, confirmed by histopathological examination. Necessary care in therapeutic interventions is discussed based on the case.	Expansion of NMO spectrum diseases associated with autoimmune diseases.
Recurrent myelitis in localized scleroderma	Masakazu Miyamoto, Masako Kinoshita, Keiko Tanakac, Masami Tanaka.	2014	MEDLINE	Case report	Report a case of a Japanese man diagnosed with cutaneous sclerosis in childhood and, as an adult, he presented symptoms compatible with transverse mileitis, on a recurring basis.	The diagnosis of transverse myelitis was confirmed by MRI, but negative NMO-IgG and visual symptoms compatible with NMO leave open its diagnosis, which is even more unlikely possible.	Case of recurrent myelitis as a complication of EL. The gap between diseases reinforces the need to monitor these patients for a long time.
Systemic sclerosis in aquaporin-4 antibody-positive longitudinally extensive transverse myelitis	Diego Franciotta, Elisabetta Zardini, Roberto Caporali, Laura Piccolo, Elisa Alberici, Alfredo Romani, Roberto Bergamaschi, Enrico Marchioni, Mauro Ceroni, Giovanni Piccolo.	2012	Scopus	Case report	Report the case of a 62-year-old woman, positive NMO-IgG, longitudinal transverse myelitis and ES.	The patient had neurological symptoms compatible with transverse myelitis (confirmed by MRI) and Raynauld's phenomenon, sclerodilty and nonspecific pulmonary fibrosis.	Expansion of NMO spectrum diseases associated with autoimmune diseases, emphasizing the need for NMO-IgG measurement in patients with autoimmune disorders.

Caption: MRI: nuclear magnetic resonance; NMO-IgG: anti-aquaporin 4; NMO: neuromyelitis optica; ES: systemic scleroderma; EL: localized scleroderma.
Source: own authors (2020)

biopsy was compatible with LS. Six months after the initial evaluation, the patient presented lower-limb paraparesis, constipation, and urinary retention, sensory level on T3, grade 0 strength in the lower limbs, and positive Babinski sign in bilateral extension. No eye complaints were reported. MRI showed a demyelinating lesion in the spinal cord, and anti-NMO was positive, confirming the diagnosis of NMOSD. The patient underwent pulse therapy with 1 g methylprednisolone for 5 days, 1 g cyclophosphamide, 2g/kg immunoglobulin, and plasmapheresis. After 14 days of hospitalization, a slight improvement in symptoms was observed[19].

The small number of viable articles selected for the final analysis of this review, and the fact that all were case reports is an indicator of the rarity of research on the association between NMO, SS, and LS. Other studies confirm this rarity, such as a Brazilian study performed with 22 patients with NMO, in which only one patient presented Raynaud's phenomenon, with no description of SS or LS. The positivity of NMO–IgG antibodies within the sample was the most significant finding, as expected. However, antinucleosome, antinuclear, antithyroperoxidase, and antithyroglobulin antibodies were limited to a small number of patients[23]. In an extensive literature review that retrieved articles from 1976 to 2017 dealing with NMO-associated autoimmune diseases, only three cases of SS/LS were found[24].

Concluding the present integrative review, it is understood that NMO–IgG is present in many different autoimmune and immune-mediated diseases. However, the association between NMO, SS, and LS is seldom described in the available medical literature researched, reaching the level of a rarity. This can be explained by the infrequent NMO-IgG testing of patients with other autoimmune diseases, as well as the also infrequent investigation of other autoimmune diseases in patients with NMO[23]. Furthermore, as observed in the reported cases, sometimes the manifestations of these diseases can occur years apart[19,24], and even if they are suspected, not all the necessary criteria for their diagnosis may be present. This may be attributable to the use of immunosuppressive medications[20], which is common in these patients, or it may be because of an early stage of NMO, which may continue to be without seropositivity or exuberant clinical manifestations[24].

In view of the results reported in the articles included in this integrative review, it is understood that it is important to intensify efforts to conduct further research with designs that are capable of capturing more data in addition to those analyzed in this review. It would also be prudent and timely to investigate the association of NMO with other autoimmune and immune-mediated diseases, given the vast field of study and research available.

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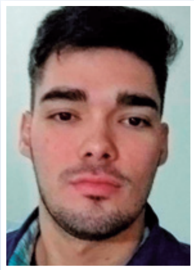
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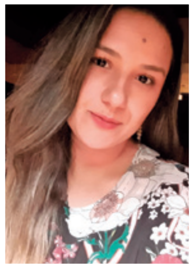
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